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COLLOIDAL URANIUM

I. TOXICITY

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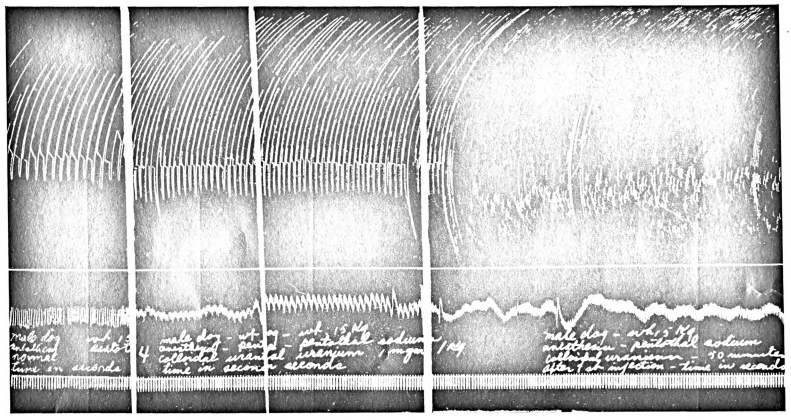
Since 1854 when Leconte (1) reported his observations on the action of uranium salts several investigators have studied the nephrotoxic and hepatoxic action of these compounds. A comprehensive survey of the literature was published in *Physiological Reviews* by MacNider (2) who, himself, has made extensive and significant contributions to the subject. From these investigations the danger incident to the administration of uranium salts is generally recognized. The purpose of this study was to determine the effect of colloidal uranium in the light of the known action of uranium nitrate. The present report is limited to the problem of toxicity.

METHOD

Effects on blood pressure and respiration. Dogs were anesthetized with pentothal sodium, 45 mgm. per kilogram of a 5 per cent solution administered intraperitoneally and prepared in the usual manner for recording of respiration and carotid blood pressure. Colloidal uranium (0.1 per cent solution) was administered intravenously via the femoral vein in doses of 1 mgm. per kilogram at intervals of ten minutes. In all cases six such doses were given to each animal and continuous tracings were taken on a long paper kymograph. With the exception of a regularly recurring slight and transitory fall in the carotid pressure about one and one-half minutes after each injection, the blood pressure changes were virtually negligible. In some instances there was a slight change in the amplitude of respiration but usually the rate as well as amplitude remained unmodified. After the fifth

or sixth injection (50 to 60 minutes) there developed a marked degree of respiratory stimulation which continued indefinitely and with increasing vigor and intensity similating the bellows-like action of salyrgan and other proteinates of mercury on anesthetized dogs. This peculiar type of respiration never shows apnea from hyperventilation. Death results usually from sheer exhaustion.

Control experiments with no medication other than the usual anesthetic and with uranium nitrate showed that this late respiratory effect was due not so much to changes in the depth of



Normal | 40 minutes after | 60 minutes after | 110 minutes after

FIG. 1. EFFECT OF COLLOIDAL URANIUM ON RESPIRATION AND CAROTID BLOOD PRESSURE

anesthesia resulting from gradual release through detoxification as to a peculiar allergic-like action-complex attributable directly to the colloidal uranium which is being further investigated.

Synchronous with the hyperventilation the blood pressure exhibited a rhythmic rise and fall; the tonicity of the cardiac musculature remained unchanged but the degrees of the contractions were diminished. The graphic records presented in figure 1 are typical.

MacNider (3) et al. have made the observation that immature animals are more resistant to uranium salts than mature animals.

In view of this fact 4 kittens were given daily subcutaneous doses of 1 mgm. per kilogram colloidal uranium and a fifth an equal daily dose of uranium nitrate. Kittens 1 and 5 were littermates one and one-half months old and kittens 2, 3 and 4 were littermates one month old. The weight of each was recorded daily at the same hour. The results are presented in table 1.

Since the toxic action of uranium on the viscera is somewhat delayed in its onset, our next step was to determine the effect of different quantities of colloidal uranium administered as single doses. Fifty mice were divided into four groups and the members within each group were given 5, 10, 15 and 20 mgm. per kilogram doses, respectively. An equal number, used as controls, for each of the above groups was given correspondingly similar doses of

TABLE 1

Kittens given 1 mgm. per kilogram daily

NUMBER	DRUG	DOSE	INITIAL WEIGHT	FINAL WEIGHT	DURATION OF LIFE
		mgm./kgm.	*kgm.*	*kgm.*	*days*
1	Colloidal uranium	1	0.65	0.37	34
2	Colloidal uranium	1	0.35	0.3	27
3	Colloidal uranium	1	0.57	0.36	24
4	Colloidal uranium	1	0.46	0.38	22
5	Uranium nitrate	1	0.63	0.45	28

uranium nitrate. Table 2 gives the comparative daily vital results. It will be observed that for the duration of the experiment (ten days) the survivals in the various colloidal uranium groups ranged between 80 and 100 per cent as against those in the control group (uranium nitrate) which dropped to 30 and 10 per cent in the 5 and 10 mgm. per kilogram groups and 0 per cent in the 15 and 20 mgm. per kilogram groups. Those in both groups that survived the ten experimental days were apparently fully recovered.

Another series of experiments with the same objective as the above was carried out on guinea pigs.

Four groups of 5 animals were given single doses of 1, 5, 10 and 15 mgm. per kilogram of colloidal uranium respectively,

in each group. No restrictions were made as to the amount of water and food. The weight of each animal was taken at the same hour daily. On the ninth day the experiment was terminated. Surviving animals were sacrificed at that time and sections of liver and kidney tissues from each were fixed to be studied histologically. As controls, an equal number of animals were divided into corresponding groups and treated with uranium nitrate. All injections were made subcutaneously. The results are presented in table 3.

TABLE 2

Comparative toxicity of colloidal uranium and uranium nitrate in single doses in mice

NUMBER	DRUG	DOSE	NUMBER OF ANIMALS	DAILY DEATHS										ALIVE AFTER 10TH DAY
				1	2	3	4	5	6	7	8	9	10	
		mgm./kgm.												
1	Colloidal uranium	5	10	0	1	0	0	0	0	3	1	0	1	4
	Uranium nitrate	5	10	0	0	1	1	3	0	4	1			0
2	Colloidal uranium	10	10	0	1	2	1	0	0	4	0	0	1	1
	Uranium nitrate	10	10	0	0	0	4	3	0	2	1			0
3	Colloidal uranium	15	15	0	1	1	0	1	1	1	0	0	0	10
	Uranium nitrate	15	15	0	3	0	2	3	6	1				0
4	Colloidal uranium	20	15	0	1	0	2	1	3	0	0	0	0	8
	Uranium nitrate	20	15	0	1	2	5	2	5					0

An analytical study of table 3 shows that 15 mgm. per kilogram colloidal uranium killed 2 of 5 guinea pigs on the eighth day, 10 mgm. per kilogram killed 3 of 5 on the seventh, eighth, and ninth day respectively, 5 mgm. per kilogram killed 1 of 5 on the ninth day, 1 mgm. per kilogram proved sublethal for all of 5 during the nine experimental days. We feel safe in stating that the animals in groups 1 and 2 that survived the ninth day would have functionally overcome the effects of the drug. They all looked well and some were showing gradual gains in weight. On the other hand uranium nitrate in all the dosage levels (1 to

TABLE 3

DAY	COLLOIDAL URANIUM					URANIUM NITRATE				
	Animal number with daily weight									
	1	2	3	4	5	1	2	3	4	5
I. 1 mgm. per kilogram of each as a single dose										
1	485	470	465	460	420	480	470	450	435	515
2	490	455	470	435	415	485	450	390	405	510
3	495	455	475	430	410	495	445	365	375	500
4	Sunday							Died		
5	490	460	485	405	360	455	415		Died	440
6	485	455	475	385	355	445	395(s)			425(s)
7	475	460	460	390	355	440				
8	480	460	470	390	360	Died				
9	485	465	470	410	360					
10	All alive, sacrificed for histological study of liver and kidneys					All dead. 2 and 5. S = sacrificed. in moribund condition for histological study of liver and kidneys				
II. 5 mgm. per kilogram of each as a single dose										
1	505	555	775	530	530	580	580	550	595	550
2	500	560	750	525	520	560	580	565	585	550
3	490	545	755	530	520	520	515	530	565	545
4	Sunday									
5	475	520	750	485	505	450(s)	475	470(s)	515	475(s)
6	465	525	740	470	500		465		490	
7	460	530	710	455	490		Died		Died	
8	460	545	700	435	485					
9	465	550	675	415	475					
				Died						
10	One died (No. 4) all other sacrificed for histological study of liver and kidneys					All dead. 1, 3 and 5. S = sacrificed in moribund condition for histological study of liver and kidneys				
III. 10 mgm. per kilogram of each as a single dose										
1	585	595	674	575	580	675	655	810	670	640
2	570	580	635	570	550	640	615	805	625	625
3	555	590	610	570	545	625	580	755	615	615
4	Holiday						Died		Died	
5	505	580	575	565	505	555(s)		680		Died
6	475	575	550	565	500			685		
7	Died	570	530	545	480			660(s)		
8		565	515	540	Died					
9		565	Died	540						
10	1, 3 and 5 died on the 7th, 9th and 8th days respectively. Two and four were sacrificed for tissues. They were in fair condition					2, 4 and 5 died on the 3rd, 4th, and 5th days respectively. 1 and 3. S = sacrificed in a moribund condition for histological study of liver and kidneys				

TABLE 3—*Concluded*

DAY	COLLOIDAL URANIUM					URANIUM NITRATE				
	Animal number with daily weight									
	1	2	3	4	5	1	2	3	4	5
	IV. 15 mgm. per kilogram of each as a single dose									
1	475	465	465	485	465	535	525	510	540	550
2	475	435	435	465	470	520	485	485	515	515
3	470	430	440	470	455	510	465	495	525	500
4	Holiday									
5	445	Died	405	455	420	480	385	465	Died	445
6	425		390	445	400	480	Died	470		Died
7	400		375	450	385	460		450		
8	385		Died	450	375	Died		400		
9	385			450	375			Died		
	2 and 3 died on the 8th day					All died				

15 mgm. per kilogram) proved 100 per cent lethal. Deaths began on the fourth day and no animal lived up to the ninth day in any of the four groups.

A fourth series of experiments was carried out on cats. Of 10 mature cats grouped in pairs of approximately equivalent weight the first four pairs were given either 5 or 10 mgm. per kilogram each of colloidal uranium or uranium nitrate. Of the fifth pair one was given 10 mgm. per kilogram of the colloidal preparation while the other was used as a normal control. Although there was provided an excess of food and water all the treated animals as early as the third day showed some weight loss. By the sixth day one of the four uranium nitrate cats was dead, one was dying and the remaining two were ematiated and in a moribund state. The colloidal uranium group at that time were all eating and drinking but not maintaining their initial weights. On that date all the members of the uranium nitrate group and three corresponding members of the colloidal uranium group were sacrificed and samples of liver and kidney tissues were taken for histological study. On the fifteenth day the two remaining members of the colloidal uranium group were still alive. The one receiving 5 mgm. per kilogram had regained

and exceeded its initial weight; the other receiving 10 mgm. per kilogram was still below its initial weight. Both appeared to be in good condition. On this day they along with the control were sacrificed in order to obtain tissues for histological study.

Grossly, the result of these studies discloses the fact that the colloidal preparation is less toxic, systemically, than the salt of uranium.

Studies on histological and functional changes during treatment are now in progress and will be reported shortly.

SUMMARY

The gross toxic effects of colloidal uranium are studied in the light of the known actions of uranium nitrate:

1. In doses of 1 mgm. per kilogram administered at intervals of ten minutes five or six times, colloidal uranium exerts no significant effect on the blood pressure or respiration.

2. Administered in daily doses of 1 mgm. per kilogram to kittens it produces a gradual weight loss leading to death within three weeks to one month.

3. As a rule animals can tolerate a single dose of 1 to 5 mgm. per kilogram. This was found to be the case with mice, guinea pigs, kittens and cats.

4. Colloidal uranium is distinctly less toxic than uranium nitrate to the organism as a whole.

We wish to express thanks to the Farnsworth Laboratories for generously supplying the colloidal uranium (coluranium) used in this study.

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